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EXAMINER

NEGIN, RUSSELL SCOTT

ART UNIT

PAPER NUMBER

1631

NOTIFICATION DATE

DELIVERY MODE

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ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

<b>Office Action Summary</b>	<b>Application No.</b> 09/784,674	<b>Applicant(s)</b> SHANNON ET AL.	
	<b>Examiner</b> RUSSELL S. NEGIN	<b>Art Unit</b> 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 22 January 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-25,27-40 and 102-165 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,5-13,15-24,30-32,37-40,102-115,119-135 and 139-165 is/are rejected.
- 7) ☒ Claim(s) 14,25,27-29,33-36,116-118 and 136-138 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Comments***

Applicants' amendments and request for reconsideration in the communication filed on 22 January 2008 are acknowledged and the amendments are entered.

Claims 1, 2, 5-25, 27-40, and 102-165 are pending and examined in this Office action. ALL of the prior art rejections are NEWLY applied.

### ***Withdrawn Objections/Rejections***

The objections to claims 6 and 148 because of informalities are withdrawn in view of amendments to the instant set of claims filed on 22 January 2008.

The rejection of claims 1, 10, 15, 16-22, 37, 39-40, 122, 124, 126-132, and 139-145 under 35 U.S.C. 103(a) as being unpatentable over Southern et al. [Nucleic Acids Research, 1994, volume 22, pages 1368-1373] in view of Southern [Current Opinion in Biotechnology, 1996, volume 7, pages 85-88] in view of Drmanac et al. [Genomics, volume 4, pages 114-128, 1989] is withdrawn in view of arguments on page 21-24 of the Remarks filed on 22 January 2008.

The rejection of claims 2, 11-13, 102-104, 106-112, 119-121, 123, 146-151, and 153-156 under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. and further in view of Southern et al. [Genomics, 1992, volume 13, pages 1008-1017] is withdrawn in view of arguments on page 21-24 of the Remarks filed on 22 January 2008.

The rejection of claims 5, 6, 23-24, 30-32, 105, 125, 133-136, 157, and 159-165 under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. and further in view of Petersheim et al. [Biochemistry, 1983, volume 22, pages 256-263] is withdrawn in view of arguments on page 21-24 of the Remarks filed on 22 January 2008.

The rejection of claims 105, 113-115, and 158 under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. in view of Southern et al. (1992) and further in view of Petersheim et al. is withdrawn in view of arguments on page 21-24 of the Remarks filed on 22 January 2008.

The rejection of claims 8-9 under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (1994) in view of Southern (1996) in view of Drmanac et al. and further in view of McMahon et al. [US Patent 5,310,650] is withdrawn in view of arguments on page 21-24 of the Remarks filed on 22 January 2008.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 33-36, 116-118, 130, 136-138, and 164 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

While the independent claims of the instant invention are drawn to a computational (i.e. *in silico*) method and apparatus, it is unclear as to how these dependent claims, which require physical laboratory steps, are performed when the base method is computational.

### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 5-25, 27-40, and 102-165 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The following analysis of facts of this particular patent application follows the analysis suggested in the “Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility”. Note that the text of the Guidelines is italicized.

To satisfy section 101 requirements, the claim must be for a practical application of the § 101 judicial exception, which can be identified in various ways (Guidelines, p. 19):

- The claimed invention “transforms” an article or physical object to a different state or thing.
- The claimed invention otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

In the instant case, the claimed invention does not “transform” an article or physical object to a different state or thing because the claimed methods and apparatus are drawn to a computation for selecting hybridization nucleotides. This does not preclude the subject matter to be patentable as, for eligibility analysis, as

*physical transformation “is not an invariable requirement, but merely one example of how a mathematical algorithm [or law of nature] may bring about a useful application.” AT&T, 172 F.3d at 1358-59, 50 USPQ2d at 1452. If the examiner determines that the claim does not entail the transformation of an article, then the examiner shall review the claim to determine if the claim provides a practical application that produces a useful, tangible and concrete result. In determining whether the claim is for a “practical application,” the focus is not on whether the steps taken to achieve a particular result are useful, tangible and concrete, but rather that the final result achieved by the claimed invention is “useful, tangible and concrete.” The claim must be examined to see if it includes anything more than a § 101 judicial exception. If the claim is directed to a practical application of the § 101 judicial exception producing a result tied to the physical world that does not preempt the judicial exception, then the claim meets the statutory requirement of 35 U.S.C. § 101. If the examiner does not find such a practical application, the examiner has determined that the claim is nonstatutory. (Guidelines, p. 20)*

The question is thus whether the final result achieved by the claimed invention satisfies all three criteria of being useful, and concrete, and tangible.

Furthermore, the useful, tangible, and concrete result must be recited in the claim itself, rather than addressed in specification.

The instant claims are drawn to computational means for selecting hybridization nucleotides. However, as claimed, the method does not produce a tangible result. For example, the method as claimed may take place entirely within the confines of a computer or a human mind without any communication to the outside world and without using or making available for use, the results of the computation. In this instance, while the last step of each independent claim recites outputting of results in a machine-

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readable and/or human readable format, the machine-readable format may not necessarily be accessible to users in which case the result of the instant set of claims are not tangible.

Furthermore, while the system claimed in claims 146 and 147 is a statutory apparatus, the method executed by this system is not statutory for the reasons discussed above.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

#### **35 U.S.C. 103 Rejection #1:**

Claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145, 157, 159-163, and 165 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. [Human Mutation, volume 7, 1996, pages 244-255] in view of Hyndman et al. [Biotechniques, volume 20, 1996, pages 1090-1095].

Claims 1 and 122 are independent claims drawn to computer based methods of selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. They involve examining and/or clustering of oligonucleotides in order to predict hybridization efficiencies.

Claim 1 has the feature of using staggered nucleotide sequences, each of the same length.

Claim 122 has the feature of using nucleotide sequences, each of the same length.

The article of Cronin et al. investigates cystic fibrosis mutation detection by hybridization to DNA probe arrays. Specifically, Figure 1 on page 245 of Cronin et al. shows the tiled array claimed in step (a) of claim 1 and claim 122. The tiled array is described in the first sentence of the second column of page 246, which states, "The tiled array described here interrogates 107 nucleotides consisting of the 95 coding bases of CFTR exon 11, plus 1 nucleotide from the 5' intron and 11 nucleotides from the 3' intron." Consequently, the 107 nucleotides of the CFTR exon are interrogated using non identical nucleotides of identical length (of bases) that are spaced one nucleotide apart.

Figure 2 on page 249 of Cronin et al. illustrates the fluorescence intensity of the tiled probe set hybridizing to the sequence in question.

Figure 3A on pages 250 of Cronin et al. illustrates a subset of the oligonucleotides within the predetermined number of non-identical oligonucleotides based on an examination the fluorescence parameter. These nucleotides are selected from among the hybridization nucleotides in figure 2 of Cronin et al. The caption of Figure 3 of Cronin et al. selects a single sequence from among the nucleotides in the cluster. The results are output in human readable form to the figures listed in Cronin et al.

Cronin et al. fails to teach the "computer aspects" to the instant set of data (i.e. computer determination of hybridization intensities).

Hyndman et al. teaches software to determine optimal oligonucleotide sequences based on hybridization simulations data. The objective of the study is to design better arrays of sequences of oligonucleotides for hybridization with a target sequence.

Claims 5 and 6 are further limiting wherein the parameter is selected from a list comprising the composition factor of sequence information content. Figures 2 and 3 of Cronin et al. illustrate the sequence content information used to help determine the hybridization.

Claim 10 is further limiting wherein said parameter is derived from a factor by mathematical transformation of said factor wherein said factor is predictive of the ability

of an oligonucleotide to hybridize with a target nucleotide sequence. The mathematical transformation of the hybridization to a fluorescence intensity as shown in Figure 2 of Cronin et al. illustrates such a mathematical transformation.

Claim 15 is further limiting wherein said parameters are determined for said oligonucleotides by means of a computer program.

Hyndman et al. teaches software to determine optimal oligonucleotide sequences based on hybridization simulations data. The objective of the study is to design better arrays of sequences of oligonucleotides for hybridization with a target sequence.

Claims 17 and 21 are further limiting wherein the oligonucleotides and the target oligonucleotides are DNA. The abstract of Cronin et al. along with Figure 2 of Cronin et al. illustrate the use of DNA for hybridization and as the target sequence.

Claims 24 and 133 are further limiting wherein the step of selecting a subset of oligonucleotides is accomplished by setting a cut off values for parameters determining the number of oligonucleotides in each cluster.

Claim 38 is further limiting comprising identifying a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides by establishing cut-off values for each of said parameters.

Figure 2 of Cronin et al. illustrates such a fluorescent cut-off for determining hybridization; the caption for figure 2 states that: ““N” is used to designate nucleotide

positions with hybridization intensities that do not meet algorithm criteria.." which is a teaching for a cutoff value for a parameter.

Claims 37 and 139 are further limiting comprising including oligonucleotides that are adjacent to oligonucleotides in said subset that are clustered along a region of said a target nucleotide sequence.

The clusters in Figure 3 are adjacent to one another in a single region of the oligonucleotide in which the schematic of the Figure counts the bases.

Claim 124 is described because all of the limitations of claim 1 are described by Cronin et al.; claim 124 recites limitations governing the tiled array recited in instant claim 1.

Claim 125 is further limiting wherein said parameter is selected from the group comprising composition factors.

Figures 2 and 3 of Cronin et al. illustrate the sequence content information used to help determine the hybridization.

Claim 126 is further limiting comprising selecting a subset of said oligonucleotides. Claim 127 is further limiting wherein said subset consists of any number of oligonucleotides with the cluster of oligonucleotides. Claim 128 is further limiting wherein the subset of clustered nucleotides is selected to statistically sample the

cluster. These limitations are also part of instant claim 1; see discussion of instant claim 1 and Figures 2 and 3 of Cronin et al. for teachings (i.e. statistical) of sampling the tiled arrays from clusters of arrays.

Claim 129 is further limiting wherein said parameters are determined for said oligonucleotides by means of a computer program.

Claims 143-145 and 163 are all further limiting requiring computational limitations to the instant set of claims.

Hyndman et al. teaches software to determine optimal oligonucleotide sequences based on hybridization simulations data. The objective of the study is to design better arrays of sequences of oligonucleotides for hybridization with a target sequence.

Claims 131 and 132 are further limiting comprising using DNA as the target and hybridized oligonucleotide. The abstract of Cronin et al. along with Figure 2 of Cronin et al. illustrate the use of DNA for hybridization and as the target sequence.

Claim 157 is claim 6 in independent form, but only incorporating as subset of the limitations of instant claim 1. Claims 159-162 are dependent from claim 157 incorporating the additional limitations from claim 1 that are not part of the subset of limitations recited in claim 157.

Since the limitations of claims 1 and 6 are taught by Cronin et al., as set forth above, the limitations of claims 157, and 159-162 are also taught by Cronin et al.

Claim 165 is further limiting comprising using DNA as the target and hybridized oligonucleotide. The abstract of Cronin et al. along with Figure 2 of Cronin et al. illustrate the use of DNA for hybridization and as the target sequence.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the tiled array studies of Cronin by the use of the hybridization simulation software of Hyndman et al. wherein the motivation would have been that Hyndman et al. teaches a software package that automates and makes more efficient the identification and design of hybridization sequences that bind to a target [see abstract on page 1090 of Hyndman et al.]

35 U.S.C. 103 Rejection #2:

Claims 18-20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145, 155-157, 159-163, and 165 above, in further view of Southern et al. [Nucleic Acids Research, 1994, volume 22, pages 1368-1373]. This article is referred to as "Southern et al. (1994)."

Claims 18-20 and 22 are further limiting reciting use of RNA and chemically modified nucleotides.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach use of RNA, chemically modified moieties, or chemicals attached to surfaces.

The article of Southern et al. (1994), states in its abstract, "Arrays of oligonucleotides corresponding to a full set of complements of a known sequence can be made in a single series of base couplings in which each base in the complement is added in turn."

Southern (1994) recites both DNA, RNA and modified oligonucleotides at the bottom of column 2 on page 1369.

It would have been obvious of someone of ordinary skill in the art at the time of the instant invention to modify the DNA tiled array study of Cronin et al. and the computerized oligonucleotide selecting of Hyndman et al. by use of the RNA tiled array study of Southern et al. (1994) because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, it would have been obvious to substitute the RNA tiled arrays for the DNA tiled arrays because both studies yield analogous results in terms of clusters of hybridization. There would have been a reasonable expectation of success in combining the studies because the nucleic acid studies are generally applicable to each other with no negative limitation regarding the species of nucleic acid in the tiles arrays.

It would have been further obvious to modify the DNA in the method of Cronin et al. and Hyndman et al. by use of the modified, synthetic oligonucleotides of Southern et al. (1994) wherein the motivation would have been that the chemically modified

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oligonucleotides of Southern et al. (1994) provide more efficient probes with isotopic labels that make the probes more easily detectable.

35 U.S.C. 103 Rejection #3:

Claims 2, 11-13, 39-40, 102-109, 111-113, 120, 121, 123, 140-143, 148-153, 155-156, and 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145 157, 159-163, and 165 above, in view of Southern et al. [Genomics, 1992, volume 13, pages 1008-1017]. This article is referred to as "Southern et al. (1992)."

Claim 2 is dependent from claim 1 with the additional limitation of ranking said oligonucleotides based on the number in said clusters.

Claim 11 is dependent from claim 1 with the additional limitation of ranking said oligonucleotides based on the number in said clusters and selecting a subset of said clustered oligonucleotides.

Claim 12 depends from claim 11 with the additional limitation of said subset comprises any number of oligonucleotides within said cluster.

Claim 13 recites statistically sampling a cluster of oligonucleotides.

Claims 39-40, 120-121, and 140-141 are further limiting requiring counting of contiguous nucleotides of predetermined length in the region in question.

Claims 102 and 148 are drawn to a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. This claim

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contains all of the elements of claim 122 with the additional embodiment of ranking the oligonucleotides.

Claims 103-108 depend from claim 102 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

Claims 111-112 depend from claim 102 with the extra limitation of claiming the species of oligonucleotide comprises DNA.

Claims 113 is further limiting wherein there is a cut-off value for establishing the clusters.

Claim 123 is dependent from claim 122 with the additional limitation of ranking said oligonucleotides based on the number in said clusters.

Claims 149-152 depend from claim 148 with the extra limitation of claiming specific types of cluster ranking and properties of the clusters.

Claims 155-156 depend from claim 148 with the extra limitation of claiming the species of oligonucleotide comprises DNA.

Claim 158 is dependent from claim 157 with the additional limitation of ranking said oligonucleotides based on the number in said clusters.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach ranking of the nucleotides.

The article of Southern et al. (1992), entitled, "Analyzing and comparing nucleic acid sequences by hybridization to arrays of oligonucleotides: evaluation using experimental models," tabulates on page 1013 in Tables I and II the ranks of clusters

illustrated in Figure 5 on page 1013 of Southern et al. (1992) and ranks with dimensionless scores of sequences within each cluster. The ranking of the oligonucleotides stops at the number 5 as a cut off in each cluster shown in Tables 1 and 2 of page 1013 of Southern et al. The ranks listed in Southern et al. (1992) also serve to count the number of nucleotides of predetermined length in a given cluster.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the DNA tiled array study of Cronin et al. and Hyndman et al. by use of the ranking analysis in Southern et al. (1992) wherein the motivation would have been that ranking the degrees of hybridization gives one of ordinary skill in the art a more complete picture of how to design sequences that would hybridize to a given sequence [see Tables I and II on page 1013 of Southern et al. (1992)].

35 U.S.C. 103 Rejection #4:

Claims 7, 23, 30-32, and 134-135 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. and Hyndman et al. as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-38, 122, 124-129, 131-133, 139, 144-145 157, 159-163, and 165 above, in view of Petersheim et al. [Biochemistry, 1983, volume 22, pages 256-263].

Claim 7 is further limiting comprising thermodynamic parameters.

Claim 23 is further limiting with the additional limitation that for each oligonucleotide/target nucleotide duplex, the difference between the predicted duplex melting temperature and the temperature of hybridization is chosen.

Claim 30 is further limiting comprising the parameter of free energy of binding.

Claims 31, 32 and 135 are further limiting with restrictions on the lengths of the oligonucleotides in the subsequences.

Cronin et al. and Hyndman et al. make obvious use of clusters in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach the relevant thermodynamic parameters.

The article of Petersheim et al, entitled, "Base-stacking and base-pairing contributions to helix stability: thermodynamics of double-helix formation with CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp," states in the first sentence of the introduction, "Due to development of rapid sequencing techniques, there has been an explosion in our knowledge of nucleic acid sequences. This understanding provides a foundation for understanding the functions and mechanisms of these macromolecules."

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Consequently, thermodynamic parameters, including the G+C content of the sequences listed are examined, and duplex formation parameters.

The length of each oligonucleotide in Petersheim et al. are within the ranges recited in claims 31, 32, and 135.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the DNA tiling array of Cronin et al. and Hyndman et al. by use of the thermodynamic analysis in Petersheim et al. wherein the motivation would have been that such thermodynamic parameters would have given useful information on the design and stability of the hybridization in each tiling array [see Figures 2-5 of Petersheim et al.].

35 U.S.C. 103 Rejection #5:

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1-2, 5-6, 10-13, 15, 17, 21, 24, 37-38, 102-109, 111-113, 122-129, 131-133, 139, 142-145 157, 159-163, and 165 above, in view of McMahon et al. [US Patent 5,310,650].

Claims 8 and 9 are further limiting reciting kinetic properties and coupling efficiencies of the hybridizations.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach the relevant kinetic parameters.

The invention of McMahon et al, entitled, "Method and device for improved reaction kinetics in nucleic acid hybridizations," teaches kinetics and coupling efficiencies of hybridizations in column 13 (Table 1) for improved binding assays.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al. and Hyndman et al. by use

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the kinetic analysis of McMahon et al. because it is obvious to improve a known technique with a known method. In this instance, McMahon et al. applies to hybridization methods the use and study of both kinetics and hybridization efficiencies to result in a more efficient and improved assay to apply to the tiled array of Cronin et al.

35 U.S.C. 103 Rejection #6:

Claims 114-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al. in view of Southern et al. (1992) as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-40, 119-122, 124-129, 131-133, 139, 140-141, 144-145, 155-163, and 165 above, and further in view of Petersheim et al.

Claim 114-115 are further limiting requiring the parameters to comprise the thermodynamic parameter of free energy and the lengths of the oligonucleotides.

Cronin et al., Hyndman et al., and Southern et al. make obvious the clustering and ranking in tiled probe arrays, as discussed above.

Cronin et al., Hyndman et al., and Southern et al. fail to teach the relevant parameter of free energy.

The article of Petersheim et al, entitled, "Base-stacking and base-pairing contributions to helix stability: thermodynamics of double-helix formation with CCGG, CCGGp, CCGGAp, ACCGGp, CCGGUp, and ACCGGUp," states in the first sentence of the introduction, "Due to development of rapid sequencing techniques, there has been an explosion in our knowledge of nucleic acid sequences. This understanding

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provides a foundation for understanding the functions and mechanisms of these macromolecules.”

Equations 1 through 5 on page 257 of Petersheim et al. provide the guidelines behind the thermodynamic parameters (free energy, melting temperature, entropy, and enthalpy) of duplex formation shown in Figures 2-6 on page 258-259 of Petersheim et al.

Consequently, thermodynamic parameters, including the G+C content of the sequences listed are examined, and duplex formation parameters.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the DNA tiling arrays of Cronin et al., Hyndman et al., and Southern et al. (1992) by use of the thermodynamic analysis in Petersheim et al. wherein the thermodynamic parameters of Petersheim et al. would have given useful information on the design and stability of the hybridization in each tiling array [see Figures 2-5 of Petersheim et al.].

35 U.S.C. 103 Rejection #7:

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1-2, 5-6, 10-13, 15, 17, 21, 24, 37-38, 102-109, 111-113, 122-129, 131-133, 139, 142-145 157, 159-163, and 165 above, in view of Anderson et al. [Introduction to Statistics, New York: West Publishing Company, 1991, pages 64-65] .

Claim 14 is further limiting wherein said statistical sample consists of oligonucleotides spaced at the first quartile, median, and third quartile of the cluster of oligonucleotides.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach quartiles.

Pages 65-66 of Anderson et al. teach the dividing of data into four quartiles.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al. and Hyndman et al. by use of the quartiles in Anderson et al. wherein the motivation would have been that the data would have been divided into four equal sets [see page 65 of Anderson et al] for ease of analysis; e.g. for computing a median, as set forth on p. 65 of Anderson. One of skill in the art would reasonably have expected success in dividing the data of Cronin et al. and Hyndman et al. into quartiles, as taught by Anderson et al., because the method taught by Anderson et al. is a common statistical technique which may be applied to any data set.

35 U.S.C. 103 Rejection #8:

Claims 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1-2, 5-6, 10-13, 15, 17, 21, 24, 37-38, 102-109, 111-113, 122-129, 131-133, 139, 142-145 157, 159-163, and

165 above, in view of Anton [Elementary Linear Algebra, New York: John Wiley and Sons, 1987, pages 35-37].

Claim 25 is further limiting wherein said step (c) comprises identifying a subset of oligonucleotides within said predetermined number of non-identical oligonucleotides by converting the values of said parameter into a dimensionless number by determining a dimensionless score for each parameter resulting in a distribution of scores having a mean value of zero and a standard deviation of one. Claim 27 is further limiting comprising optimizing a method according to calculation for said parameter on said individual scores.

Consequently, optimizing the results of the tiled array into an identity matrix fits the limitations of these dependent claims.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach identity matrices with dimensionless data.

Anton is a textbook for linear algebra.

Pages 35-37 of Anton et al. teach the use and properties of identity matrices.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al. and Hyndman et al. by use of the linear algebra calculations in Anton wherein the motivation would have been that identity matrices have unique properties in terms of data analysis [see pages 35-37 of Anton] applicable to the results of the instantly rejected claims.

35 U.S.C. 103 Rejection #9:

Claims 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1-2, 5-6, 10-13, 15, 17, 21, 24, 37-38, 102-109, 111-113, 122-129, 131-133, 139, 142-145 157, 159-163, and 165 above, in view of Edwards et al. [An Introduction to Linear Regression and Correlation; New York: W.H. Freeman and Company, 1984, pages 24-26] .

Claim 28 is further limiting comprising determining at least two parameters wherein the absolute value of a correlation coefficient between said parameters is less than 0.5. Claim 29 is further limiting wherein said parameters are derived from a combination of factors by mathematical transformation of those factors.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to teach regression coefficients.

Edwards is a textbook on regression analysis.

Section 3.2 on page 25 of Edwards teaches the theory behind correlation coefficients and illustrates a weak correlation of 0.33 in panel d of Figure 3.1.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al. and Hyndman et al. by use of the correlations in Edwards wherein the motivation would have been that the correlation coefficient in Edwards illustrates a convenient metric to which association between different variables can be assessed [see first paragraph of section 3.2 on page 25 of

Edwards]. It would have been further obvious to optimize the correlation as the optimization would have resulted in a single factor from a combination of factors [i.e. see section 3.3 on page 26 of Edwards].

35 U.S.C. 103 Rejection #10:

Claims 16, 130, and 164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al., as applied to claims 1-2, 5-6, 10-13, 15, 17, 21, 24, 37-38, 102-109, 111-113, 122-129, 131-133, 139, 142-145 157, 159-163, and 165 above, in view of Goldberg et al. [US Patent 5,959,098, issued 28 September 1999; filed 17 April 1996] .

Claims 16, 130, and 164 are further limiting wherein the oligonucleotides are attached to a surface.

Cronin et al. and Hyndman et al. make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al. and Hyndman et al. fail to attachment of the oligonucleotide to a surface.

Figure 1 of Goldberg et al. teaches attachment of oligonucleotides to surfaces.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al. and Hyndman et al. by use of the oligonucleotide attachment to substrates on Goldberg et al. wherein the motivation would have been that the attachment of the oligonucleotides to a substrate would have

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resulted in an array capable of being processed in a high throughput, high quality, and lower costing method [see column 1 , lines 43-50 of Goldberg et al.].

35 U.S.C. 103 Rejection #11:

Claims 110 and 154 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al. in view of Southern et al. (1992) as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-40, 119-122, 124-129, 131-133, 139, 140-141, 144-145, 155-163, and 165 above, and further in view of Goldberg et al.

Claims 110 and 154 are further limiting wherein the oligonucleotides are attached to a surface.

Cronin et al., Hyndman et al., and Southern et al. (1992) make obvious the computerized cluster analysis in tiled arrays, as discussed above.

Cronin et al., Hyndman et al., and Southern et al. (1992) fail to attachment of the oligonucleotide to a surface.

Figure 1 of Goldberg et al. teaches attachment of oligonucleotides to surfaces.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al., Hyndman et al., and Southern et al. (1992) by use of the oligonucleotide attachment to substrates on Goldberg et al. wherein the motivation would have been that the attachment of the oligonucleotides to a substrate would have resulted in an array capable of being processed in a high throughput, high quality, and lower costing method. [see column 1 , lines 43-50 of Goldberg et al.].

35 U.S.C. 103 Rejection #12:

Claims 116-118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al. in view of Southern et al. (1992) in view of Petersheim et al. as applied to claims 1, 5-6, 10, 15, 17, 21, 24, 37-40, 119-122, 124-129, 131-133, 139, 140-141, 144-145, 155-163, and 165 above, and further in view of Goldberg et al.

Claims 116-118 are further limiting wherein the oligonucleotides are attached to a surface with a given number of bases between the subsequence and the terminus attached to the substrate.

Cronin et al., Hyndman et al., Southern et al. (1992), and Petersheim et al. make obvious the computerized cluster analysis in tiled arrays and the thermodynamics of the relevant arrays, as discussed above.

Cronin et al., Hyndman et al., Southern et al. (1992) and Petersheim et al. fail to show the required attachment of the oligonucleotide to a surface with the appropriate, recited distances.

Figure 1 of Goldberg et al. teaches attachment of oligonucleotides to surfaces. Furthermore, the sequences of Petersheim et al. are each six nucleotides in length and consequently fit the description of the limitations in the instant set of claims relevant to the number of bases from a free end attached to a substrate and a sequence.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al., Hyndman et al., Southern et

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al. (1992), and Petersheim et al. by use of the oligonucleotide attachment to substrates on Goldberg et al. wherein the motivation would have been that the attachment of the oligonucleotides to a substrate would have resulted in an array capable of being processed in a high throughput, high quality, and lower costing method. [see column 1 , lines 43-50 of Goldberg et al.].

35 U.S.C. 103 Rejection #13:

Claims 33-36 and 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al. in view of Hyndman et al. in view of Petersheim et al. as applied to claims 1, 5-7, 10, 15, 17, 21, 23-24, 30-32, 37-38, 122, 124-129, 131-135, 139, 144-145 157, 159-163, and 165 above above, and further in view of Goldberg et al.

Claims 33-36 and 136-138 are further limiting wherein the oligonucleotides are attached to a surface with a given number of bases between the subsequence and the terminus attached to the substrate and energy of each oligonucleotide probe is minimized.

Cronin et al., Hyndman et al., and Petersheim et al. make obvious the computerized cluster analysis in tiled arrays and the thermodynamics of the relevant arrays with minimized energies, as discussed above.

Cronin et al., Hyndman et al., and Petersheim et al. fail to show the required attachment of the oligonucleotide to a surface.

Figure 1 of Goldberg et al. teaches attachment of oligonucleotides to surfaces.

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Furthermore, the sequences of Petersheim et al. are each six nucleotides in length and consequently fit the description of the limitations in the instant set of claims relevant to the number of bases from a free end attached to a substrate and a sequence.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the tiling arrays of Cronin et al., Hyndman et al. and Petersheim et al. by use of the oligonucleotide attachment to substrates on Goldberg et al. wherein the motivation would have been that the attachment of the oligonucleotides to a substrate would have resulted in an array capable of being processed in a high throughput, high quality, and lower costing method. [see column 1, lines 43-50 of Goldberg et al.].

### ***Response to Arguments***

Applicant's arguments with respect to the instant claims have been considered but are moot in view of the new ground(s) of rejection.

It is noted that while several of the secondary references are reiterated in this rejection, applicant's arguments were concerned with the primary combination of Southern et al. (1994), Southern et al. (1996), and Drmanac et al. used in the previous rejection that is now withdrawn in view of arguments. The primary reference in the current set of rejections is Cronin et al., which is newly applied.

### ***Conclusion***

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/  
Russell S. Negin, Ph.D.  
10 May 2008

/Marjorie Moran/  
Supervisory Patent Examiner, Art Unit 1631